REMARKS

In the Office Action mailed March 18, 2003, claims 1-7 and 24 were rejected under 35 U.S.C. 112, first paragraph. The Examiner is thanked for a telephone interview on June 5, 2003 in which the 35 U.S.C. 112, first paragraph rejection of claims 1-7 and 24 was discussed. In the telephone interview, the Examiner indicated a more specific listing of conditions treated with the compounds of the invention was required. This response amends claims 1 and 24 to specifically list the conditions treated with the compounds of the invention. This amendment complies with 37 C.F.R. 1.116, and is believed to place the case in condition for allowance.

The Amendments

Claims 1 and 24 have been amended for clarity. Support for the amendments to claim 1 are found in the specification as filed, for example page 13, lines 13-16 (cataracts and retinopathy); page 1, lines 33-35 (retinal cell damage); and page 1, line 37 through page 2, line 2 (lens and retinal cell damage). Support for the amendments to claim 24 are found in the specification as filed, specifically: loss of PKC in eye lens cells (page 31, lines 19-page 32, line 7; page 32, lines 9-24), polyol accumulation in the eye (page 32, lines 13-15), galactitol formation from galactose in lens cells (page 27, line 5 through page 28, line 11), vascular leakage in the eye (page 29, lines 25-30), and expression of aldose reductase in the retina (page 26 through page 27, line 4; page 13, lines 17-18). No new matter is added by any amendment, and all amendments are supported by the specification as filed.

35 U.S.C. 112, first paragraph rejection

In the Office Action mailed March 18, 2003, claims 1-7 and 24 were rejected under 35 U.S.C. 112, first paragraph. The Office Action stated "the specification while being enabling for certain disorders of diabetic complications, polyol accumulation, galactitol formation and expression of aldose reductase, does not reasonably provide enablement for the broad phrases of 'a diabetic complication', 'polyol accumulation', 'galactitol formation' and 'expression of aldose reductase' . . .Applicant fails to provide information allowing the skilled artisan to ascertain the above conditions without undue experimentation. The instant claims read on all 'diabetic complications, all symptoms of 'polyol accumulation', all symptoms of 'galactitol formation', all

conditions of 'expression of aldose reductase', necessitating an exhaustive search for the embodiment suitable to practice the instant invention."

The inventors of the present invention have invented a new group of compounds that treat ocular complications of diabetes. Diabetes is a disease that causes well-known and well-defined ocular complications (page 1 line 32 through page 3 line 2). These ocular complications cause cataracts, lens cell damage, retinal cell damage, retinopathy and blindness. Measurable parameters in the eye that indicate the presence of diabetic ocular complications include loss of PKC in eye lens, polyol accumulation in the eye, galactitol formation from galactose in lens, vascular leakage in the eye, and expression of aldose reductase in the retina (see Exhibit A).

In response to the statement that "the instant claims read on all 'diabetic complications,'" it is noted that the term "diabetic complication" is not used in the claims. Before the current amendment, claim 1 recited "a diabetic complication in the eye" (emphasis added). As discussed above, diabetic complications in the eye are well-defined and extensively studied (see Exhibit A - National Eye Institute, Pathophysiology Section, "Preventing Ocular Complications of Diabetes" <http://www.nei.nih.gov/intramural/patho2.htm>). Claim 1 now recites a method of preventing cataracts, retinopathy, lens cell death and retinal cell death caused by diabetes comprising administering a compound of the invention. It is believed claim 1 now specifically lists the conditions prevented with the compounds of the invention.

In response to the statement in the Office Action that the claims read on all symptoms of "polyol accumulation", all symptoms of "galactitol formation", all conditions of "expression of aldose reductase", necessitating an exhaustive search for the embodiment suitable to practice the instant invention, it is noted that polyol accumulation, galactitol formation and expression of aldose reductase are easily measurable parameters in the eye that occur when eye damage caused by diabetes is present, not diseases that have multiple symptoms. Polyol accumulation, galactitol formation and expression of aldose reductase are easily studied, as described in the present specification. For example, testing for polyol accumulation is described on page 25, lines 25-26: "cells are tested for polyol accumulation by GC/mass spectroscopy". Testing for formation of

galactitol is described in the specification on page 27. Testing for aldose reductase inhibition is described on page 26. Claim 24 has been amended to specify the parameters that were actually tested using the compounds of the invention, as shown by the examples in the specification referred to above.

The Office Action states that the specification is enabling for certain disorders of diabetic complications, polyol accumulation, galactitol formation and expression of aldose reductase. In the Interview with the Examiner, it was determined that more specific terminology should be used. In view of the above arguments and amendments, the terminology used in the claims enables one of ordinary skill in the art to practice the instant invention without undue experimentation. Administration of the compounds listed in the claims results in improvement in the parameters listed in the claims, as shown by the examples in the specification. Reconsideration and withdrawal of the rejection is respectfully requested. At the very least, claim 24 should be allowable, since it specifically lists parameters described in the specification which were tested using the compounds of the invention.

CONCLUSION

It is believed that all rejections are overcome and the application is ready for allowance. Reconsideration and withdrawal of the rejections is respectfully requested. If there are any issues remaining, the Examiner is respectfully requested to telephone the undersigned.

It is believed that the present submission does not require the payment of any fees. If this is incorrect however, please charge any fees required, including any extensions of time required, to Deposit Account No. 07-1969.

Respectfully submitted,

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Pathophysiology Section

Preventing Ocular Complications Of Diabetes

The primary cause of ocular complications of diabetes is an elevated level of plasma glucose. The excess glucose causes flux through the polyol pathway, which results in a marked increase in aldose reductase (AR) activity and the accumulation of sorbitol, the polyol of glucose, in all tissues that do not require insulin for glucose uptake. Polyol accumulation is a common denominator between the hyperglycemia of diabetes and galactosemia. High dietary galactose (30% to 62%) results in more AR activity and a greater accumulation of polyol (galactitol) than does diabetes (Figure 1), probably due to the almost fourfold higher affinity of AR for galactose than for glucose and because galactitol, unlike sorbitol, is not metabolized (Figure 2). Evidence that polyol accumulation is a critical factor is supported by the observation that the galactose-fed rat develops retinal vascular lesions that appear to be indistinguishable from those observed in human diabetic retinopathy. Thus, the galactose-fed rat makes a very reliable and convenient model of diabetic retinopathy and other ocular complications for testing pharmacological compounds as possible therapeutic agents.

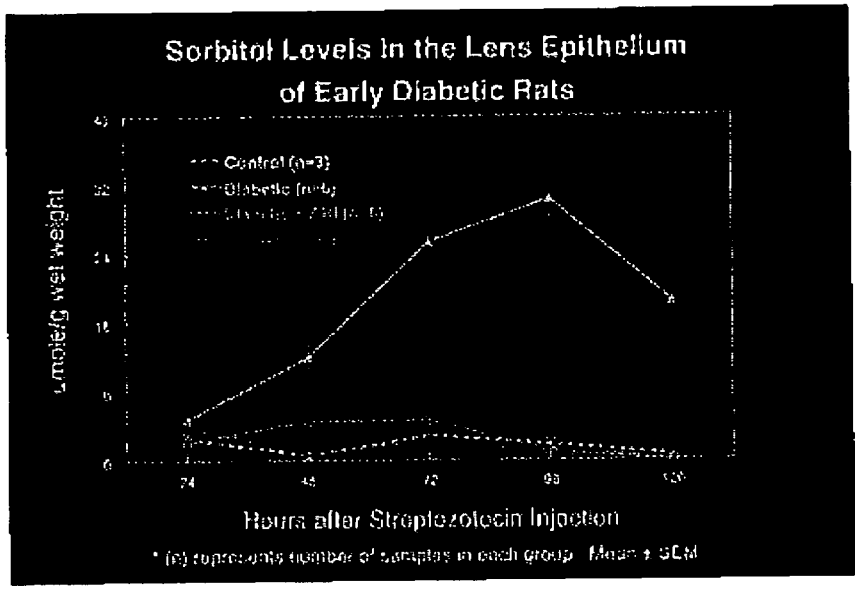

Figure 1A. Rapid Polyol Accumulation in Lens Epithelium:
Sorbitol in rats rendered diabetic by streptozotocin injection [- - - - - - - - - - - - nondiabetic (n = 3); ——▲—— diabetic (n = 6); ——○—— diabetic plus the aldose reductase inhibitor AL-1576 (n = 6); —— nondiabetic plus AL-1576 (n = 1)].

Pathophysiology Section (continued)

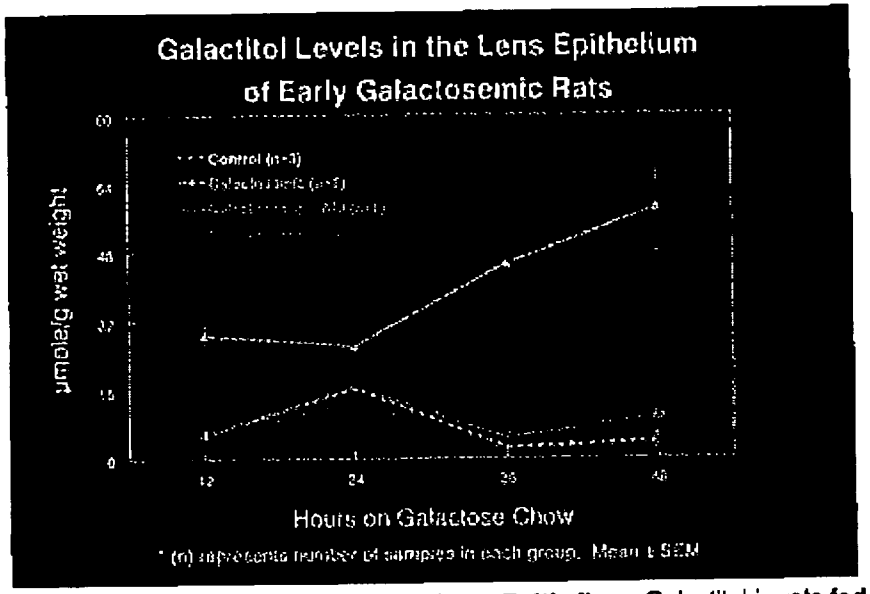

Figure 1B. Rapid Polyol Accumulation in Lens Epithelium: Galactitol in rats fed a 30% galactose diet ····· nongalactosemic (n = 3); ——◊—— galactosemic (n = 6); ——♦—— galactosemic plus AL-1576 (n = 6); and —— —— —— nongalactosemic plus AL-1576 (n = 1)]. The AR1, AL-1576 (4 mg/kg/day), was administered every 24 hr by gavage. (Robison, W.G., Jr., Laver, N.M. and Lou, M.F.: The role of aldose reductase in diabetic retinopathy: prevention and intervention studies. p. 593-640. In Osborne, N.N. and Chader, G.J. (Eds.): Progress in Retinal and Eye Research v. 14, Oxford, Pergamon, 1995).

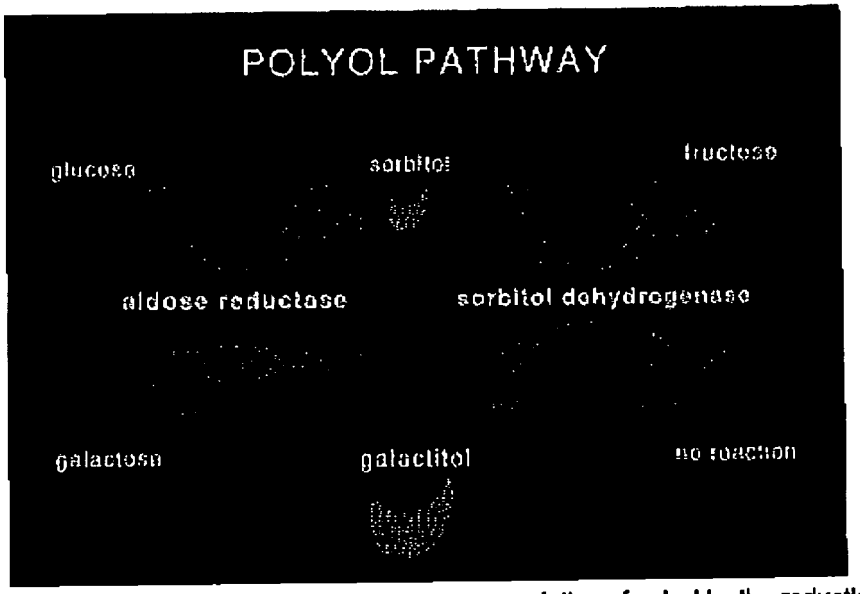

Figure 2. Polyol Pathway: There is a greater accumulation of polyol by the reduction of galactose than glucose owing to the higher affinity of aldose reductase for galactose than for glucose and the fact that there is no subsequent metabolism of galactitol. (Robison, W.G., Jr. and Laver, N.: Ocular lesions in animal models of human diabetes. p. 145-163. In Shafrir, E. (Ed.): Frontiers in Diabetes Research, Lessons from Animal Diabetes IV. London, Smith-Gordon and Company Limited, 1993).

In the galactose-fed rat model of diabetic ocular complications, diabetic-like cataracts develop within 2 to 3 weeks; corneal sensitivity is significantly decreased by 4 weeks; both diabetic-like thickening of retinal capillary basement membranes and degeneration of intramural pericytes occur by 16 to 24 weeks. Severe non-proliferative to proliferative retinopathy develops by 96 weeks. Included at these stages are capillary dilations, microaneurysms, intraretinal microvascular abnormalities (IRMA), and some intra- and extraretinal neovascularization. All these lesions, which appear to be indistinguishable from those that occur in human diabetic retinopathy, are prevented in the galactose-fed rat model by treatment with an aldose reductase inhibitor (ARI). These findings are illustrated and summarized in the following brief comments, figures, and legends.

October 1997

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